

Request for permission for oral testimony at Idaho
Medicaid's P&T Committee meeting on 05-20-2011

Submission # 2

The following request has been:

- ☐ Approved
- ☒ Denied

Gennrich, Jane - Medicaid

From: Eide, Tamara J. - Medicaid
Sent: Friday, May 06, 2011 10:40 AM
To: Gennrich, Jane - Medicaid
Subject: FW: Your Request for Medical Information
Attachments: Letter.PDF; - CAYSTON® US Prescribing Information, February 2010.pdf; - Customer Satisfaction Survey.pdf

Tami Eide, Pharm.D., BCPS

Medicaid Pharmacy Program Supervisor/Manager
Idaho Department of Health and Welfare
eidet@dhw.idaho.gov
3232 Elder St.
Boise, ID 83705
208-364-1829
800-327-5541 fax

From: Alfred Ngaw [mailto:Alfred.Ngaw@gilead.com] **On Behalf Of** Medical Information
Sent: Thursday, May 05, 2011 6:24 PM
To: Eide, Tamara J. - Medicaid
Subject: Your Request for Medical Information

To Dr. Eide,

Please find attached the Medical Information you requested. (PDF files require Adobe Acrobat Reader: www.adobe.com). We value your opinion of our written response(s) to your question(s). Your feedback will help us evaluate and continually improve the quality of our service. Please take a minute to complete a short, five question, anonymous survey <http://www.zoomerang.com/Survey/WEB22BDSRQRUHP>. No personal information will be accessed or utilized from the survey.

Regards,

Gilead Sciences, Medical Information

THIS COMMUNICATION IS CONFIDENTIAL AND INTENDED
FOR THE PERSON OR ENTITY TO WHOM IT IS ADDRESSED



May 5, 2011

Tami Eide, Pharm.D.
Idaho Dept of Health
3232 Elder Street
Boise, ID 83705

Dear Dr. Eide:

Thank you for your request related to CAYSTON®. Please see the enclosed package insert for full prescribing and safety information.

Enclosed please find the requested information in response to your inquiry related to CAYSTON and its active comparator trial clinical results.

- Oermann et al.² conducted and presented a phase 3, open label, randomized, 6 month international trial of 3 on/off courses of aztreonam for inhalation solution (AZLI) in patients with CF and pulmonary *Pseudomonas aeruginosa* (PA) infection using tobramycin inhalation solution (TIS) as an active comparator. The objective of the study was to evaluate safety and efficacy of AZLI over time compared to the existing standard of care treatment.
 - AZLI was statistically superior to TIS with respect to
 - Adjusted mean relative change in FEV₁ % predicted at 28 days.
 - Adjusted mean actual change in FEV₁ % predicted over 3 “on/off” cycles.
 - Mean change in CFQ-R Respiratory Symptom Score was significantly higher with AZLI than TIS.
 - Additionally, AZLI was associated with fewer pulmonary exacerbations, demonstrated by:
 - Fewer respiratory hospitalizations
 - Fewer events requiring IV and/or inhaled antipseudomonal antibiotics
 - AZLI AEs over the 3 treatment courses were consistent with previously published clinical trial experiences.

CAYSTON® is indicated to improve respiratory symptoms in cystic fibrosis (CF) patients with *pseudomonas aeruginosa*. Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV₁ <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*. To reduce the development of drug-resistant bacteria and maintain the effectiveness of CAYSTON and other antibacterial drugs, CAYSTON should be used only to treat patients with CF known to have *Pseudomonas aeruginosa* in the lungs.

Gilead Sciences, Inc. is providing this document in response to your unsolicited request for medical information. Some of the data included in this response may be outside of the U.S. Food and Drug Administration (FDA)-approved Prescribing Information for the referenced products. Gilead Sciences, Inc. does not intend to offer an opinion regarding the clinical relevance of these data or the advisability of administering any drug in a manner inconsistent with its approved labeling.

Please report all adverse events, following or coincident with the use of any Gilead product to Gilead Sciences Drug Safety and Public Health at 1-800-445-3235, option 3, or to the FDA MedWatch Program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), by mail (MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787) or via the internet <http://www.accessdata.fda.gov/scripts/medwatch>.

We hope this information has been helpful to you. Patricia Bourne, PharmD [(559) 280-4967 Patricia.Bourne@gilead.com], a Medical Scientist from Gilead Sciences, may follow-up with you to ensure this information addressed your inquiry.

If you have any additional questions, please contact Gilead Medical Information toll free at 1-800-GILEAD-5 (select option 2) or email medicalinformation@gilead.com.

Sincerely,

Alfred Ngaw, Pharm.D., BCPS
Senior Manager, Medical Information
Gilead Sciences

ANGAW/ANGAW/3154

Delivery Method: E-Mail

Encl: - CAYSTON® US Prescribing Information, February 2010
 - Customer Satisfaction Survey

IMPORTANT NOTE: Gilead Sciences, Inc. is providing this document in response to your unsolicited request for medical information. Some of the data included in this response may be outside of the U.S. Food and Drug Administration (FDA)-approved Prescribing Information for the referenced products. Gilead Sciences, Inc. does not intend to offer an opinion regarding the clinical relevance of these data or the advisability of administering any drug in a manner inconsistent with its approved labeling.

ACTIVE COMPARATOR TRIAL: CAYSTON AND TOBRAMYCIN INHALATION SOLUTION, CLINICAL RESULTS

This trial is the first clinical trial to explore the comparative safety and efficacy of Cayston and tobramycin inhalation solution in adult and pediatric cystic fibrosis patients with pulmonary *Pseudomonas aeruginosa* infection.

CAYSTON is indicated to improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*. Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV₁ <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*. To reduce the development of drug-resistant bacteria and maintain the effectiveness of CAYSTON and other antibacterial drugs, CAYSTON should be used only to treat patients with CF known to have *Pseudomonas aeruginosa* in the lungs.¹

OVERVIEW

- Oermann et al.² conducted and presented a phase 3, open label, randomized, 6 month international trial of 3 on/off courses of aztreonam for inhalation solution (AZLI) in patients with CF and pulmonary *Pseudomonas aeruginosa* (PA) infection using tobramycin inhalation solution (TIS) as an active comparator. The objective of the study was to evaluate safety and efficacy of AZLI over time compared to the existing standard of care treatment.
 - AZLI was statistically superior to TIS with respect to
 - Adjusted mean relative change in FEV₁ % predicted at 28 days.
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 - Mean change in CFQ-R Respiratory Symptom Score was significantly higher with AZLI than TIS.
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 - Fewer respiratory hospitalizations
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CLINICAL DATA

Background

Inhaled antipseudomonal antibiotics are the standard of care for cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (PA) airways infection. Tobramycin inhalation solution (TIS) was approved by the Food and Drug Administration in 1997 for the management of CF patients with chronic pulmonary PA infection. Cayston was approved by the FDA in 2010 to improve respiratory symptoms in CF patients with PA. A 6-month active comparator trial with Cayston and TIS was required for full marketing approval in the European Union (EU) and Canadian was a post-marketing commitment in the United States.²

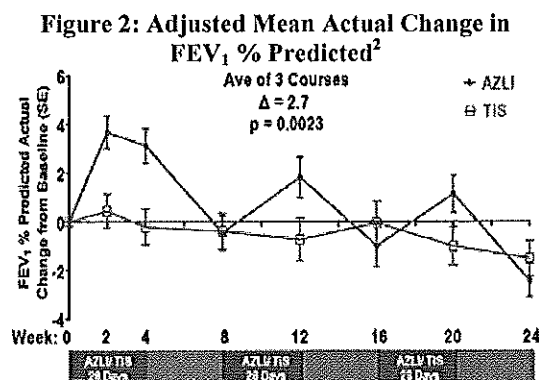
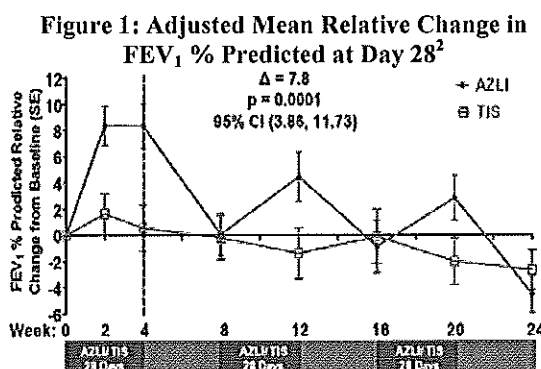
Study Design and Population

The objective of the study (ClinicalTrials.gov identifier GS-US-205-0110) was to evaluate the comparative safety and efficacy of Cayston and TIS in adult and pediatric CF subjects with pulmonary PA infection. The trial design was a phase 3, open label, randomized, parallel, 6 month international trial of 3 on/off courses at 91 CF centers in the EU and the US. The patients were ≥6 yrs, with baseline FEV₁ ≤75% predicted, chronic PA infection and stable pulmonary disease. Patients were randomized 1:1 to receive

aztreonam for inhalation solution (AZLI) 75 mg TID via Pari Investigational eFlow® Nebulizer System (now commercially available as Altera® Nebulizer System) or TIS 300 mg BID via Pari LC Plus nebulizer for 3 cycles (28 days on/28 days off). Prior to randomization, the patient population was stratified according to TIS use in the prior 12 months, < 84 days or ≥ 84 days. The < 84 days TIS cohort was capped at 40 patients. Co-primary endpoints were 1) non-inferiority of AZLI for mean % change in FEV₁ % predicted at Day 28 (per EMA), and 2) superiority of AZLI for mean actual change in FEV₁ % predicted across three treatment cycles (per FDA requirement). Additional endpoints consisted of pulmonary exacerbation as indicated by need for anti-pseudomonal antibiotics or respiratory hospitalization, mean change in CFQ-R Respiratory Symptom Scale (RSS) score, mean change in sputum *PA* density, and frequency of adverse events (AE). Two hundred and seventy-three patients were randomized, with 268 patients treated (AZLI=136; TIS=132).² The two groups were well matched in terms of age, gender, inhaled tobramycin use in 12 months prior to randomization, FEV₁ % predicted at baseline, CFQ-R RSS at baseline, log₁₀ *PA* colony forming units (CFU) at baseline, and number of patients with multidrug resistant *PA*.^{2,3}

Efficacy Results

The adjusted mean relative difference in FEV₁ % predicted at day 28 for the AZLI group versus the TIS group was 7.8 ($P = .0001$, 95% CI 3.86-11.73), and thus met one co-primary endpoint (non-inferiority at day-28; week 4 data of figure 1).² The adjusted mean actual difference in FEV₁ % predicted across three treatment cycles for the AZLI group versus the TIS group was 2.7 ($P = .0023$), and thus met the other co-primary endpoint, superiority to TIS across 3 treatment cycles (week 24 data of figure 2).²



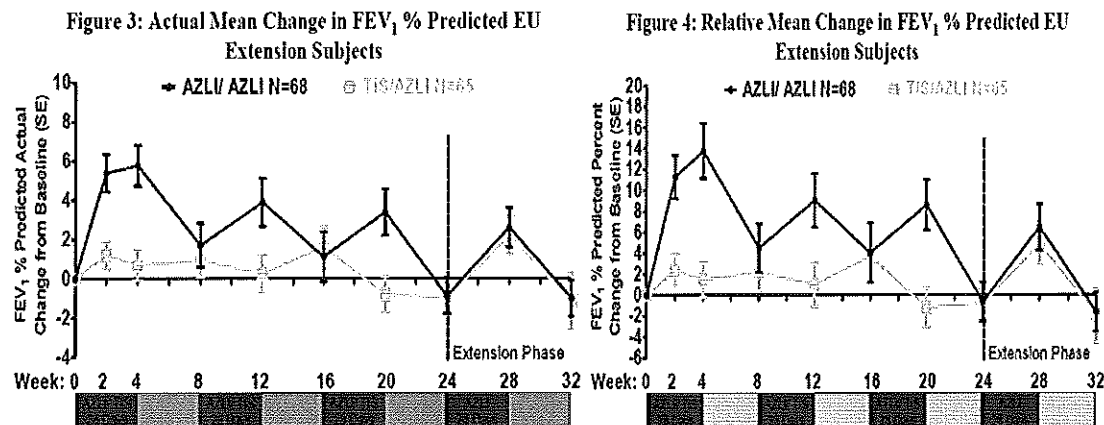
The subgroup of patients who were regular users of TIS (≥ 84 days in the prior 12 months) had a lower adjusted mean relative change in FEV₁ % predicted compared to the overall AZLI group. The change over the three courses was 7.5 ($P = .0002$). This result was similar in magnitude for mean actual change in FEV₁ % predicted, which was 3.5 ($P = .0002$).²

There was a 31% reduction ($P = .044$; AZLI 40 cases, TIS 58 cases) in respiratory hospitalizations. There was also a 31% reduction ($P = .004$; AZLI 84 cases, TIS 121 cases) in related respiratory events requiring IV and/or inhaled antipseudomonal antibiotics. The adjusted mean change (AZLI minus TIS) in CFQ-R RSS scores from baseline to the completion of 3 courses was 4.1 points ($P = .0189$, minimal clinically important difference = 4 points). There was not a statistically significant difference in adjusted mean change in sputum log₁₀ *PA* CFU between AZLI and TIS. During the trial there were no significant changes in *PA* susceptibilities to aztreonam or other antibiotics, and no significant emergence of other respiratory pathogens. The treatment compliance (as measured by the % of vials inhaled) was very similar for the two treatment groups. The AZLI treatment group were 94.0 % compliant (standard deviation 9.55), and the TIS treatment group was 94.17 % compliant (standard deviation 10.48).²

Extension Phase Results

A 6-month open-label AZLI treatment extension phase, available to European sites only, was added to the end of the original treatment design. Data from the first extension-phase treatment cycle is available. Sixty-five TIS patients were switched to AZLI while 68 prior AZLI patients continued. Preliminary results

from the first extension phase cycle (Figures 3 and 4) demonstrates that both groups show increases in FEV₁ % predicted with AZLI, regardless of prior treatment assignment (AZLI or TIS).⁴



Safety Results

The AE profile for the randomized phase of this trial was consistent with previously published clinical trial experience. See table 1 for AEs noted in AZLI or TIS product labels as having occurred with greater frequency versus placebo in placebo-controlled trials for either drug.²

Table 1: Adverse Events by Study Drug²

AE	AZLI, n (%) (n = 136)	TIS, n (%) (n = 132)
Cough	96 (70.6)	104 (78.8)
Nasal Congestion	29 (21.3)	26 (19.7)
Wheezing	16 (11.8)	20 (15.2)
Pharyngolaryngeal pain	36 (26.5)	37 (28.0)
Pyrexia	43 (31.6)	40 (30.3)
Chest discomfort	14 (10.3)	13 (9.8)
Abdominal Pain	18 (13.2)	8 (6.1)
Vomiting	14 (10.3)	14 (10.6)
Tinnitus	2 (1.5)	1 (0.8)
Voice alteration	5 (3.7)	8 (6.1)

REFERENCES:

1. CAYSTON® (aztreonam for inhalation solution). US Prescribing Information. Gilead Sciences, Inc., Foster City, CA. Revised February 2010.
2. Oermann C, Assael B, Nakamura C, et al. Aztreonam for Inhalation Solution (AZLI) vs. Tobramycin Inhalation Solution (TIS), a 6-Month Comparative Trial in Cystic Fibrosis (CF) Patients with *Pseudomonas aeruginosa* (PA) [Poster 305 & Podium Presentation]. Paper presented at: 24th Annual North American Cystic Fibrosis Conference; October 21-23, 2010; Baltimore, Maryland.
3. Oermann C, Assael B, Nakamura C, et al. Aztreonam for Inhalation Solution (AZLI) vs. Tobramycin Inhalation Solution (TIS), a 6-Month Comparative Trial in Cystic Fibrosis (CF) Patients with *Pseudomonas aeruginosa*. *Pediatr Pulmonol*. Oct 2010;Suppl 33:327.
4. Data on File, Gilead Sciences, Inc.

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